Complete Summary

GUIDELINE TITLE

Venous thromboembolism (VTE).

BIBLIOGRAPHIC SOURCE(S)

University of Michigan Health System. Venous thromboembolism (VTE). Ann Arbor (MI): University of Michigan Health System; 2009 Feb. 13 p. [10 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: University of Michigan Health System. Venous thromboembolism (VTE). Ann Arbor (MI): University of Michigan Health System; 2004 Aug. 11 p. [5 references].

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 3, 2008 - Innohep (tinzaparin): The U.S. Food and Drug Administration (FDA) has requested that the labeling for Innohep be revised to better describe overall study results which suggest that, when compared to unfractionated heparin, Innohep increases the risk of death for elderly patients (i.e., 70 years of age and older) with renal insufficiency. Healthcare professionals should consider the use of alternative treatments to Innohep when treating elderly patients over 70 years of age with renal insufficiency and deep vein thrombosis (DVT), pulmonary embolism (PE), or both.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Venous thromboembolic (VTE) disease, comprised of:

- Deep venous thrombosis (DVT)
- Pulmonary embolism (PE)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Neurology
Obstetrics and Gynecology
Oncology
Orthopedic Surgery
Pharmacology
Pulmonary Medicine
Radiation Oncology
Surgery

INTENDED USERS

Advanced Practice Nurses
Nurses
Pharmacists
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To improve the recognition of venous thromboembolism (VTE) and selection of appropriate testing for VTE
- To shorten resolution time for clinical symptoms

- To reduce incidence of pulmonary embolism
- To reduce mortality
- To reduce bleeding and other complications
- To reduce costs of hospitalization

TARGET POPULATION

Adults with suspected acute deep venous thrombosis of the lower extremity, pulmonary embolus, or both

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Diagnosis of deep venous thrombosis (DVT)
    - Clinical likelihood estimation
    - Venous color duplex Doppler ultrasound imaging
    - D-dimer assays (for exclusion in low-probability patients only)
    - Phlebography (seldom indicated)
2. Diagnosis of pulmonary embolism (PE)
    - Clinical likelihood estimation
    - D-dimer assays (with formal clinical likelihood estimation to exclude low-probability patients only)
    - Helical computer tomography (CT) (to establish but not to rule out PE)
    - Ventilation-perfusion (V/Q) scanning
    - Venous color duplex Doppler ultrasound
    - Pulmonary angiography
    - Magnetic resonance imaging (MRI) angiography (not recommended)

Treatment/Prevention/Management

1. Heparin anticoagulation
    - Heparin followed by warfarin
    - Low molecular weight heparin (LMWH)
    - Unfractionated heparin (UFH)
    - Aggressive treatment (thrombolytic therapy with tissue-type plasminogen activator [t-PA] in exceptional cases only)
2. Warfarin (Coumadin) anticoagulation
3. Inferior vena cava filters, if anticoagulation is contraindicated or has failed
4. New non-heparin anticoagulant agents (e.g., lepirudin, argatroban)
5. Use of graduated compression stockings within 2 weeks of DVT
6. Monitoring of therapy

MAJOR OUTCOMES CONSIDERED

- Duration of clinical symptoms
- Length of hospital stay
- Recurrence rate of thrombosis (pulmonary embolism [PE] or deep vein thrombosis [DVT])
- Incidence of pulmonary embolism
- Post-thrombotic syndrome

- Mortality and complication rates
- Incidence of bleeding complications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The initial prospective literature searches for this project were performed in 1996, 1997, and 2002. The current update is based on a supplemental literature search performed in January 2008. For diagnostic topic, literature published since the 2002 was searched. For treatment topics, the team accepted the literature search performed through May 2006 for the American College of Chest Physicians guideline on antithrombotic therapy for venous thromboembolic disease. Literature published since May 2006 was searched.

The population was adults. Major key words were: *pulmonary embolism and deep venous thrombosis thrombophlebitis (includes venous thromboembolism, thromboembolism, venous thrombosis), guidelines, controlled trials, meta-analyses*. Additional search terms for diagnosis were: *duplex venous scan, pulmonary angiography, ventilation perfusion (V/Q) scan, arterial blood gasses (O2 saturation), computed tomography, computed tomography (CT) angiography, CT venography, magnetic resonance imaging, D-dimer, recurrent pulmonary embolism, pulmonary hypertension–embolism, and pregnancy and venous thromboembolism (VTE) diagnosis*. Additional search terms for treatment were: *low molecular weight heparin, heparin, warfarin, international normalized ratio, prothrombin time, argatroban, lepirudin, bivalirudin, vena cava filter, temporary filter, massive pulmonary embolism (angiographic embolism removal, extracorporeal membrane oxygenation (ECMO), thrombolytic: pharmaceutical and mechanical), pregnancy and VTE treatment, and failure of therapy*. Detailed search terms and strategy are available upon request.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence for the Most Significant Recommendations

A. Randomized controlled trials
B. Controlled trials, no randomization

C. Observational trials
D. Opinion of expert panel

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if randomized controlled trials (RCTs) were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

I = Generally should be performed

II = May be reasonable to perform

III = Generally should not be performed

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

University of Michigan Health System (UMHS) guidelines are reviewed by leadership and in clinical conferences of departments to which the content is most relevant. This guideline was reviewed by the Departments of Emergency Medicine, Family Medicine, Internal Medicine (General Medicine, Cardiovascular Medicine,

and Pulmonary and Critical Care Medicine), Radiology (Nuclear Medicine), and Surgery (Vascular Surgery).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The following key points summarize the content of the guideline. Refer to the full-text guideline for additional information, including detailed information on dosing recommendations (i.e., a body weight-based intravenous heparin dosing nomogram) and test performance characteristics of ventilation perfusion (V/Q) scanning.

The strength of recommendation (I-III) and levels of evidence [A-D] are defined at the end of the "Major Recommendations" field.

Initiate Treatment Immediately

Patients without contraindications to heparin should begin full-dose heparinization at once *[IA*]*. If pulmonary embolism (PE) is clinically likely, initiation should not await testing; if only deep vein thrombosis (DVT) is suspected and testing will be prompt, initiation may await testing. Therapeutic levels of anticoagulation should be achieved as quickly as possible. Warfarin should be initiated on day 1 of treatment, after heparin loading is complete.

Diagnosis

- **Deep Venous Thrombosis**
  - Clinical likelihood estimation. Symptoms and signs alone are not adequately sensitive or specific for diagnosis or exclusion of venous thromboembolism (VTE), but clinical likelihood estimation based on symptoms and signs is a necessary step in the testing strategy. *[IA]*
  - Lower extremity DVT: Venous color duplex Doppler ultrasound imaging is the standard for diagnosis *[IA]*. Depending on the clinical likelihood estimate, high-sensitivity D-dimer testing can exclude DVT without imaging (see the original guideline document for more information).
- **Pulmonary Embolism**
  - Lab tests inadequate. D-dimer testing must be interpreted in the context of pretest probability. *[IC]* D-dimer testing alone is not adequately sensitive or specific to diagnose or exclude PE. *[IIIC]*
  - Diagnostic testing determined by clinical likelihood estimation. The diagnostic approach differs depending on prior probability (see the original guideline document for more information). Low probability patients with negative D-dimer require no further testing. *[IA]* Others should generally undergo computed tomography (CT) scanning. *[IA]* High or intermediate probability patients with negative CT or low probability patients with CT positive for sub- or segmental PE require further investigation (see the original guideline document for more information). *[IA]*

Treatment

- **Heparin**
    - Low molecular weight heparin (LMWH) preferred. LMWH is preferred over unfractionated heparin (UFH) for both safety and cost reasons *[IA]*.
    - Outpatient use of LMWH for DVT. LMWH is appropriate for most patients with DVT to use at home. *[IIA]* Some require initial brief hospital admission and stabilization; clinically stable (afebrile, normotensive, without tachycardia or tachypnea) patients who are not at elevated risk due to comorbidities can manage DVT entirely in the outpatient setting using LMWH.
    - Unfractionated heparin. If UFH is used, it should be initiated and dosed in a structured manner to achieve therapeutic levels quickly, without excessive adjustment of dosing *[IIA]*.
    - Minimum time period. Heparin (LMWH or UFH) must be continued until international normalized ratio (INR) is >2.0, but always for at least five days to minimize the risk of extension of thrombosis or occurrence or recurrence of embolism *[IB]*.
    - If heparin contraindicated. Patients who are not candidates for heparin anticoagulation due to risk of major bleeding or to drug sensitivity (heparin-induced thrombocytopenia [HIT]) may be candidates for one of the new non-heparin anticoagulant agents (e.g., lepirudin, argatroban). *[IIB]* Those who cannot use any anticoagulant should have an inferior vena cava filter placed to prevent pulmonary embolization *[IIB]*.
- **Warfarin**. Patients should begin warfarin on day one of heparin therapy after heparin loading is complete, and INRs must be >2.0 before discontinuation of heparin *[IA, B]*. Start warfarin at the anticipated therapeutic dose *[IC]*; loading doses are no longer considered appropriate. *[IIC]*
    - If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated for several months with full-dose subcutaneous heparin *[IA]*, preferably LMWH.
- **Aggressive therapy**. Patients with extensive proximal DVT producing severe limb swelling and pain, or patients with massive PE producing shock or systemic hypoperfusion may be candidates for emergent thrombolytic therapy or (in the case of DVT) thrombectomy. Such patients should be discussed with a consultant immediately. *[IID]*

Definitions:

Strength of Recommendation

I = Generally should be performed

II = May be reasonable to perform

III = Generally should not be performed

Levels of Evidence

*Levels of evidence reflect the best available literature in support of an intervention or test:

A. Randomized controlled trials
B. Controlled trials, no randomization
C. Observational trials
D. Opinion of expert panel

CLINICAL ALGORITHM(S)

The following algorithms are provided in the original guideline document:

- Diagnosis of pulmonary embolism
- Use of a ventilation perfusion (V/Q) scan in pulmonary embolism diagnosis

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is identified and graded for the most significant recommendations (see "Major Recommendations").

Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if randomized controlled trials (RCTs) were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis, treatment, and management of venous thromboembolism

POTENTIAL HARMS

- Complications of anticoagulation therapy include major bleeding, heparin-induced thrombocytopenia (HIT), and warfarin-induced skin necrosis.
- HIT is an uncommon but serious complication of heparin therapy that can cause arterial and venous thrombosis, and less often bleeding.
- Phlebography carries appreciable local morbidity, the risk of contrast administration, and is technically inadequate in 7% to 20% of studies.
- The use of inferior vena cava (IVC) filters may result in the following complications: deep venous thrombosis (DVT) at insertion site; change in filter position (tilting, migration); perforation of inferior vena cava; IVC thrombosis; local trauma to skin, vessels, and nerves at insertion site; entanglement of central venous catheters is possible with supra-renal IVC placement.
- Information on dietary sources of vitamin K which can reduce the effect of warfarin should be provided as part of patient education, as should warning about over the counter (OTC) vitamin supplementation.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Contraindications to anticoagulation include fresh surgical wound; active gastrointestinal or other bleeding (not occult blood); recent hemorrhagic cerebrovascular accident; multiple/major trauma; recent neurosurgery; and inability or unwillingness to comply with oral anticoagulation.
- Use of warfarin is contraindicated during pregnancy. Warfarin can cause birth defects.

QUALIFYING STATEMENTS

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Foreign Language Translations
Patient Resources
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Jun (revised 2009 Feb)

GUIDELINE DEVELOPER(S)

University of Michigan Health System - Academic Institution

SOURCE(S) OF FUNDING

University of Michigan Health System

GUIDELINE COMMITTEE

Venous Thromboembolism Guideline Team

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies

whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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	Research Support	Novartis

GUIDELINE STATUS

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This guideline updates a previous version: University of Michigan Health System. Venous thromboembolism (VTE). Ann Arbor (MI): University of Michigan Health System; 2004 Aug. 11 p. [5 references].

GUIDELINE AVAILABILITY

Electronic copies: Available for download (in Portable Document Format [PDF]) from the University of Michigan Health System Web site.

AVAILABILITY OF COMPANION DOCUMENTS

Continuing Medical Education (CME) information is available from the University of Michigan Health System Web site.

PATIENT RESOURCES

The following are available:

- Deep vein thrombosis. University of Michigan Health System; 2005 Feb 22. Various p. Electronic copies: Available in English and Spanish from the University of Michigan Health System Web site.
- Warfarin (Coumadin™) patient education handout. University of Michigan Health System; 2009 Jan. Various p. Electronic copies: Available from the University of Michigan Health System Web site.
- Low molecular weight heparin (LMWH) patient education handout. University of Michigan Health System; 2009 Jan. Various p. Electronic copies: Available from the University of Michigan Health System Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on May 20, 1999. The information was verified by the guideline developer on June 17, 1999. This NGC summary was updated on November 8, 2004. The updated information was verified by the guideline developer on December 7, 2004. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on July 13, 2009. The updated information was verified by the guideline developer on July 21, 2009.

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